TESTICULAR FEMINIZATION IN TWO SISTERS

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Testicular feminization is a phenotypic female with breast development and complete external genitalia and functioning vagina with male and gonadal and chromosomal sex.

Testicular feminization is not a well known inter-sex. The classical form of testicular feminization can be easily diagnosed. Though there are earlier occasional references about this condition by De Quervain (1923), Schiller (1940) and by Goldberg and Maxwell (1948). Morris (1953) has focussed special attention on this condition by reviewing 80 cases from the literature and called this condition in a male "pseudohermaphroditism as Testicular feminization". These are phenotype females with hypoplastic testes. Numerous families have been described in which several members of the family were afflicted.

Various hormonal studies have been made (Bucholtz *et al*, 1963; Drobnjak, *et al* 1963; Morris and Mahesh, 1963; and French *et al*, 1966). Excellent reviews have been written about testicular feminization Hauser (1963); Morris and Mahesh (1963); Van Wyk and Grumbach (1968); and Federman (1967).

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Case 1: (Figs. 1:2:3:4:5)

Lakshmi, an unmarried girl of sixteen years, was brought to the hospital for a painful swelling in the right inguinal region of 10 days duration and primary amenorrhoea. She was dressed up as a boy with cropped hair and shorts from her childhood, as there were no boys in the family and her parents were fond of boys. She noticed spurt of skeletal growth from the eleventh year and breast development from the age of thirteen.

Family History

The patient was the eighth child in a family of eleven girls. The first, second and fourth were the mothers of four to seven children. Each of them have only two children at present. The ninth and the tenth attained menarche at the normal age of 14 years and have been regularly menstruating for the last eight months and two years respectively. Fifth pregnancy ended in abortion. The sixth and the eighth children were cases of testicular feminization and their case reports are presented here. Lakshmi was the youngest of the two.

Patient was of an average build, height 160 cm. weight 44 Kg. Her face was smooth and free from hair over the chin, upper lip and sides of the face. The hair on the scalp was soft and luxuriant and devoid of masculine frontal alopecia. Breasts were well developed with poor areolae and small nipples.

Axillary hair and pubic hair were absent. External genitalia were normal with slight

long limbs, hands and fingers. The bone age corresponds to the actual age. X-ray pelvimetry in these cases showed a gynaecoid pelvis. Others (Witschi and Mengert, 1952; Hauser, 1963) have reported android pelvis.

Breast development is normal in spite of the presence of testes. If the testes were removed before menarche, mammary development does not occur. Postpubertal castration produces flabby breasts. Areola and nipple is poorly pigmented.

These women have attractive figures. In classical cases there is absence of sexual hair over the external genitalia and axillae and over the face. This leads to the description of hairless women with testes. In incomplete forms certain sexual hair growth may be seen. Baldness and hirustism are never seen. The hair follicles do not respond even with large doses of testosterone. Wilkins (1957) and Prader (1957) have postulated an end organ insensitivity to androgens.

The absence of hair over the vulva is striking. The vulva is either normal as in our two cases or infantile with short perineum. The vagina is normal and adequate for sexual relations. Uterus is never present. The classical character of the testicular feminization is a blind vagina. There is a direct relationship between the length of the vagina and the degree of testicular insufficiency. In incomplete forms vagina may be aplastic.

The gonads are found in the inguinal region in the majority of cases. In spite of this, inguinal hernias are rare. The gondas are located in the inguinal region in 60% of the cases (Hauser, 1963). In the rest of the cases it is equi-distributed in between the abdomen, over the side wall of the pelvis and labia majora.

The histology of the gonad shows small narrow seminiferous tubules without a lumen. It is difficult to differentiate the sertoli cells and spermatogonia. The majority of cells are undifferentiated and there are only occassional sertoli cells. Spermatogonia, and representatives of the higher stages of spermatogonia are seldom seen (Goldberg and Maxwell, 1984). In contrast, leydig's interstitial cells have been seen in all cases and they are very well developed and occasionally have undergone adenomatous proliferation. Yellow brown, finely granular pigment and occasionally Reinkes crystaloids are demonstrated in the interstitial cells.

This report confirms the clinical picture, growth pattern eunachoid tendency, common site of the gonad in the inguinal region, and histology of the gonad in the form of small seminiferous tubules and leydig cell hyperplasia.

Teter and Boczyowaski (1966) have described two types of people. A: testicular feminization without pubic hair and normal clitoris—hairless women with testes as described above, and B: testicular feminization with clitoral enlargement and pubic hair. The histology in the former group did not show any evidence of degeneration of seminiferous tubules and they showed hyperplasia of leydig cells. In cases of testicular feminization with clitoral enlargement and pubic, hair, there was sclerohyalinization of the seminiferous tubules, containing well differentiated sertoli cells, degenerated germinal elements and small nests of leydig cells were seen in the gonads.

prominence of the labia minora. Clitoris was of the normal size. Hymen was absent and vagina was capacious and admitted two fingers easily and of about six centimeters depth and adequate enough for coitus. Vagina ended blindly and the uterus was absent. On coughing two swellings of about 4 cm. x 2 cm. size were prominent over the external abdominal ring on either side. A sickening sensation was present on pressure and they were diagnosed as gonadal swellings. Other systems were normal.

Psychologically, she was a little shy individual. As the parents had reared her as a boy, she croped her hair and she was in shorts. She earned the wages of a man working along with the other men. She moved freely among them and she was teased for her masculine attire. Sexual relationship with males was satisfactory.

She found it difficult psychologically to adjust in woman's dress though she was having hetero-sexual relationship with males.

Hemoglobin was nine grams per cent. Urine was free from albumin and sugar. Blood urea was eighteen milligrams per cent and blood sugar was ninety four milligrams per cent. Seventeen ketosteroids excretion in twenty four hours urinary collection was 14.8 mgs%. Vaginal cytology showed a maturation index as 0/85/15. Peripheral blood smear and buccal smear showed absence of drum sticks in polymorphs and Bar bodies in epithelial cells. X-ray studies of the extremities showed bone age between 14 and 18 years. X-ray study of the pelvis showed a gynaecoid pelvis.

Laparotomy was done with sub-umbilical midline incision. Uterus and tubes were absent. Near the internal abdominal ring there were gonads on either side. The right gonad was about 4 cm. by 2 cm. size with thick tissue all around (Probably epididimis). The left gonad was a little smaller of about 3 cm. by 2 cm. size. Both gonads were excised. Cut section of the gonadal tissue showed yellow coloured solid area. Biopsy of the gonads revealed sparsely distributed immature seminiferous tubules, and were lined by single layer of epithelial cells with vesicular nuclei, sertoli cells. Seminiferous tubules did not show any degenerative changes. In between the tubules, there were densely distributed leydig cells in sheets. One portion of the slide showed a tendency to leydig cell adenoma formation.

Case 2 (Figs. 6, 7)

This patient was 24 years old and the 6th child of the eleven children in the family and the elder sister of the above patient. On seeing the first patient, the other members of the family were screened for testicular feminization.

She came to this hospital at the age of tenth year for a painful lump in right inguinal region which was excised.

The patient noticed breast development and somatic growth at the age of ten. She was married at the age of thirteen and since then she was leading a normal sexual life. She did not attain menarche.

She was an average built female with well developed breasts and small areolae and nipples. Skin over the face was smooth and axillary and pubic hair were absent. External genitalia were normal and clitoris was of normal size. Labia minora were slightly hypertrophied. Vagina was about 6 cm. depth and adequate for normal sexual relations. Uterus was absent. On rectal palpation, left gonad of about 3 to 4 cm. size was felt in the left side of the pelvis. Gonadal sensation was elicited on pressure.

X-ray of the pelvis showed gynaecoid pelvis. Sex chromatin in polymorph nuclear leucocyte was negative. Seventeen ketosteroids in twenty four hours urinary excretion was 15.2 mg.

Discussion

The growth and development of the patients with testicular feminization are usually normal. The breast development occurs at the normal age of puberty without the onset of menarche. Primary amenorrhoea and later sterility, and inguinal hernia and swellings, may lead the patient to consult the doctor for the first time. The patients with testicular feminization are rather tall. There is a tendency for eunachoid growth in the height with relatively

long limbs, hands and fingers. The bone age corresponds to the actual age. X-ray pelvimetry in these cases showed a gynaecoid pelvis. Others (Witschi and Mengert, 1952; Hauser, 1963) have reported android pelvis.

Breast development is normal in spite of the presence of testes. If the testes were removed before menarche, mammary development does not occur. Postpubertal castration produces flabby breasts. Areola and nipple is poorly pigmented.

These women have attractive figures. In classical cases there is absence of sexual hair over the external genitalia and axillae and over the face. This leads to the description of hairless women with testes. In incomplete forms certain sexual hair growth may be seen. Baldness and hirustism are never seen. The hair follicles do not respond even with large doses of testosterone. Wilkins (1957) and Prader (1957) have postulated an end organ insensitivity to androgens.

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Endocrine studies in these cases have shown normal or elevated levels of urinary ketosteroids of 15 to 30 mgs. in 24 hours, normal male or female levels of urinary oestrogens, cornification of the vagina, and normal or slightly elevated gonadotrophins. With castration there has been a fall in ketosteroids and oestrogens, a decrease in vaginal cornification, and a rise in gonadotrophins indicating at least in part a gonadal hormonal source. (Morris and Mahesh 1963; Hauser 1963; Zouralas and Jones 1965). Our case showed a maturation index of vaginal smear as 0/85/15, consistent with the reports of others.

Pathogenesis

The cause for testicular feminization can be due to failure of end organ response to androgen, or intrauterine testicular insufficiency. Evidence is strong to suspect it as an end organ failure to androgens.

Hauser (1957, 1963) observed that the degree of testicular insufficiency corresponds to the degree of feminization. Those cases with less affected testes and with a certain amount of development of seminiferous tubules show less classical features of testicular feminization as there is always some pubic hair, a short vagina and sometimes even hypertrophy of the clitoris. Hauser believes that testicular feminization is the inevitable consequence of early intrauterine testicular insufficiency.

Wilkins (1957) postulated that the target organs were resistant to androgens. This is the most likely cause of testicular feminization and it is supported by various studies of steroid metabolism in testicular feminization (Morris and Mahesh 1963, David *et al* 1965, Nehar 1965, Nathan Kase and Morris 1965, French *et al* 1966). Incubation of these testicular slices with labelled precursors in vitro, revealed substantial conversion to testosterone. The testosterone levels in plasma and urine are in the range of normal adult males and much higher than in the range of females. The 17-ketosteroid excretion in various studies varied from 14 mg. to 20 mg. Peripheral conversion of testosterone to estrogen has been excluded as a pathogenic mechanism (French *et al*). Wilkins first suggested that the failure of androgen sensitive target tissues to masculinize in utero, and at puberty could be explained by end organ resistance to androgen stimulation. Large doses of testosterone (Wilkins) failed to elicit any masculinising features such as growth of sexual hair, clitoral enlargement and any anabolic effects such as retention of nitrogen, phosphorus or citric acid. The android configuration of the pelvis is absent. Our cases showed a gynaecoid pelvis. The lack of germ cell maturation is due to end organ failure of the seminiferous tubules to androgens. The hypothalmic feed back mechanism similarly lacks normal sensitivity to testosterone and the hypersecretion of gonadotrophic hormone is responsible for the adenomatous leydig cell hyperplasia and a new equilibrium of FSH is maintained with oestrogens.

Newman and co-workers (1966) postulated that testosterone is blocked by circulating inhibitors and evidence for this is lacking in testicular feminization.

Genetic aspects

The familial incidence has long been recognised. Diecke (1957) described the case of testicular feminization in two sisters with different fathers. This shows that the condition is inherited from the mother. About one half of the males at risk are affected with testicular feminization (Grumback and Barr 1958, Prader 1957).

This condition is either passed on by a sex linked recessive gene manifesting in the male or a male limited autosomal dominant that provokes androgen resistance (Jacob 1959, Hauser 1963 and Philip 1965). These cases of testicular feminization are chromatin negative and have a karyotype 46/XY consistant with testes (Jacob *et al* 1959). Several workers (Stewart 1959, Puck *et al* 1960, Nilson *et al* 1959) have analysed the pedigrees of the cases of testicular feminization and its relation to colour blindness or haemophilia. In several cases the gene for testicular feminization and that for colour blindness are separately inherited. The observations of Puck *et al* (1960) indicate that carrier females had a delayed menarche and carrier mothers had pronounced reduction of sexual hair. Contrary to this the sisters of our cases had menarche at the normal age and they had normal amount of secondary sexual hair.

Transitional forms: There is an inverse relationship between the degree of testicular feminization and depth of the vagina, and the degree of maturity of seminiferous tubules. In incomplete forms of testicular feminization, there is shallow vagina with clitoral hypertrophy and even pubic hair growth and proportionate maturity of seminiferous tubules showing maturation of sertoli cells and spermatogonia (Hauser 1963).

Sexual behaviour and psychology: In spite of the presence of testes, sexual feelings are that of female. They lead a normal sexual life and fit well as a wife, as shown in our two cases.

The *diagnosis* of testicular feminization is made in primary amenorrhoeic i.e. women with good breast development, and absence of sexual hair and a functioning vagina and absence of uterus. Biopsy of the gonad proves to be a testis. An inguinal gland in a female child during repair of the inguinal hernia should lead to suspicion of testicular feminization. A biopsy of the gonad and negative sex chromatin prove the diagnosis.

Management: It depends upon the time factor when they are diagnosed either before puberty or after puberty. Castration should not be performed in a prepubertal girl as the gonad is essential for pubertal and breast development.

Neoplastic change in cryptorchoid testes is reported (Morris and Mahesh, 1963 and Hauser 1957 and 1963) and this is much more in the third decade of life. This led to the belief of prophylactic castration during the course of an exploratory laparotomy. After castration they must be kept on oestrogens to alliviate menopausal symptoms and to maintain the breast growth. However, Hauser (1963) believes that the gonads should be preserved, unless neoplastic change has occurred, for endocrine function.

Summary

1. Two cases of testicular feminization in sisters are described. They are phenotypically female with negative sex chromatin. Testis showed leydig cell hyperplasia with primitive seminiferous tubules. Clinical features, hormonal study, pathogenesis, genetics, transitional forms and management are discussed.

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See Figs. on Art Paper IV-V

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Hon. Secretaries.

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